PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Rec'd PCT/PTO 16 JUN 2005

Applicant's or agent's file reference PPD70182/WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/05450	International filing date *(day/month/year)* 09.12.2003	Priority date *(day/month/year)* 20.12.2002
International Patent Classification (IPC) or both national classification and IPC C07C253/08		
Applicant SYNGENTA LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.07.2004	24.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seelmann, M Telephone No. +49 89 2399-8335

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05450

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-7 as originally filed

Claims, Numbers

1-5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	5
Inventive step (IS)	Yes:	Claims	1-4
	No:	Claims	5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

see separate sheet

The present application relates to the preparation of γ-cyhalothrin in three steps:

a) chlorination of 1R cis-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl cyclopropanecarboxylic acid to give the corresponding acyl chloride;

b) esterification of the acyl chloride with 3-phenoxy benzaldehyde in the presence of a source of cyanide;

c) epimerization of the diastereoisomeric mixture of b).

D1 GB 2 000 764
D2 US 3 835 176
D3 US 4 183 948
D4 P. D. Bentley *et al.*, Pestic. Sci., 11, 156-164 (1980)
D5 EP 0 106 469

D1 and **D4** are cited in the present application

Novelty - Art.33(2) PCT

D1 describes the preparation of γ-cyhalothrin by esterification of of (1R)-cis-(Z)-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid with an optically active cyanohydrin (**D1**, page 3; page 4, lines 20-39; example 7; product n°1)

D4 describes the preparation of (S)-α-cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate (i.e. γ-cyhalothrin of formula (I)) by reacting the 1R cis-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl cyclopropanecarboxylic acid chloride with (R) or (S) 3-phenoxymandelamide, followed by fractional distillation and dehydratation (**D4**, structure (XIX), pages 163-164). The compound of formula (II) is known from **D1** (page 4, lines 20-27, claim 14) or **D5** (examples 3 and 4, claim 1). The compound of formula (II) is known from **D5** (examples 3 and 4, claim 1), in its racemic form from **D1** (page 4, lines 20-27, claim 14) or.

D2 discloses the preparation of α-cyanobenzyl cyclopropanecarboxylate (col.1, lines 4-43) by reacting the acyl halide of formula (IV) with the aldehyde in presence of sodium or potassium cyanide of formula (col.2, lines 41-64): step 2 of the present process.

D3 relates to the preparation of cyhalothrin by production of the acyl chloride from the

corresponding acid and reaction with an alcohol, α-cyano-3-phenoxybenzyl alcohol (examples 18-19).

D5 specifically discloses in claim 1 the mixture of : **(S)-α**-cyano-3-phenoxybenzyl (**1R,cis**)-3-(**Z**-2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcylopropane carboxylate and (R)-α-cyano-3-phenoxybenzyl (1S,cis)-3-(Z-2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcylopropane carboxylate, wherein the first mentionned corresponds to one of the two diasteroisomers of claim 5 of the present application. This specific disclosure is implicitly novelty destroying for claim 5. The fact that it is disclosed in mixture with another compound does not interfere for the question of novelty, since the skilled person knew at that time how to isolate **(S)-α**-cyano-3-phenoxybenzyl (**1R,cis**)-3-(**Z**-2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcylopropane carboxylate from the mixture. Novelty of claim 5 is accordingly not recognized in view of **D5**.

Inventive step - Art. 33(3) PCT

The closest related process to prepare γ-cyhalothrin is known from **D1**. The technical problem posed is to provide another synthetical approach to prepare γ-cyhalothrin (I) on an industrial scale without using expensive optically active reagents. The proposed solution is the process of claims 1-4, in particular step c) thereof.

The prior art process involves the use of optically active cyano phenoxybenzaldehyde or derivative thereof (**D1**, **D4**) or no optically active starting materials (**D2**, col.2-4; **D3**, examples 17-19). In the latter situation, resolution with optically active solving agents is necessary in order to isolate the final compound. The proposed epimerization avoids the use of such expensive reagents and is therefore an interesting industrial alternative. Since there is no incentive in the prior art about performing an epimerization to recover γ-cyhalothrin from the reaction mixture, an inventive activity could be recognized (claims 1 to 4).